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Critical issues in the treatment of hepatitis C virus infection in methadone maintenance patients

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Abstract

Aims—Hepatitis C virus (HCV) infection is a common chronic complication of injection drug use. Methadone maintenance programs contain large numbers of patients infected with HCV. This paper reviews HCV infection with emphasis on the medical care of HCV-infected, or HCV and human immunodeficiency virus co-infected, patients on methadone or buprenorphine maintenance.

Methods—Literature searches using PubMed, PsycINFO and SocINDEX were used to identify papers from 1990–present on antiviral therapy for HCV in methadone maintenance patients and on liver transplantation in methadone maintenance patients.

Results—Injection drug use is the most significant risk factor for HCV infection in most western countries. The prevalence of HCV antibody is high in injection drug users (53–96%) and in patients enrolled in methadone maintenance programs (67–96%). Studies of antiviral therapy for HCV in methadone maintenance patients show rates of sustained virological response (SVR), defined as negative HCV-RNA 24 weeks after the end of treatment, of 28–94%. In studies with contrast groups, no significant differences in SVR between methadone and contrast groups were found. Excellent completion rates of antiviral therapy (72–100%) were found in five of six studies. There are many barriers to methadone maintenance patients' receiving antiviral therapy, and research on overcoming barriers is discussed. Liver transplantation has been successful in methadone maintenance patients but has not been utilized widely.

Conclusion—High quality medical care for all aspects of HCV infection can be provided to methadone maintenance patients. The literature supports the effectiveness of such services, but the reality is that most patients do not receive them.

Keywords

Antiviral therapy; buprenorphine; hepatitis C; injection drug use; liver transplantation; medical care; methadone maintenance

INTRODUCTION

Hepatitis C virus (HCV) infection is a common and potentially serious chronic complication of injection drug use [1]. For patients who self-administer heroin or other illicitly used

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opiates and who have developed tolerance, methadone maintenance will be the most effective treatment [2,3]; buprenorphine/naloxone is also effective [4,5]. Methadone maintenance treatment prevents narcotic withdrawal, reduces or eliminates heroin or other opioid self-administration by people addicted to opioids and facilitates social rehabilitation. Methadone maintenance programs contain large numbers of patients infected with HCV. This paper reviews HCV infection with emphasis on the data that are most important for the medical care of HCV-infected methadone maintenance patients and includes a detailed analysis of published reports on antiviral therapy of HCV infection and liver transplantation in these patients.

METHODS

Specific searches were conducted on antiviral therapy and methadone maintenance, and liver transplantation and methadone maintenance, in January, June, October and December 2007. Searches were also conducted for antiviral therapy and injection drug use because papers on this subject may include methadone maintenance patients. Search terms used were: hepatitis C, HCV, methadone, methadone maintenance, antiviral therapy, interferon, ribavirin, injection drug use, IDU and liver transplantation.

All searches were limited to the English language and were made using PubMed (http://www.pubmed.gov); in October 2007 the searches were also conducted on PsycINFO and SocINDEX. Searches included reports from 1990–present.

We found 11 papers containing data on antiviral therapy for HCV infection in methadone maintenance patients [6–16]. We excluded one study in which some methadone maintenance patients were included in a larger group of injection drug users without delineation of specific results in methadone maintenance patients [8], two papers which were retrospective [11,12] and one [16] which did not have as a stated aim [17] the study of methadone maintenance patients. Two of the papers reported on the same patients [6,10] (the earlier study [6] reported preliminary results due to the urgent need to document feasibility of antiviral treatment in methadone maintenance patients) and are considered together. Six papers [7,9,10,13–15] were evaluated for quality items that were derived from other publications [17,18]— documentation of inclusion and exclusion criteria [17,18]; similarity of comparison groups at baseline [18]; intention-to-treat (ITT) analysis used [18]; and withdrawals and dropouts described [18]—or developed by us—comparison of methadone maintenance patients with and without a sustained virological response (SVR), defined as a negative HCV-RNA 24 weeks after the end of treatment; or a prolonged follow-up to assess for re-infection with HCV. Quality items were graded as present, partial or absent. For liver transplantation, all studies showing results of transplantation in methadone maintenance patients are included.

BACKGROUND INFORMATION ON VIROLOGY, EPIDEMIOLOGY AND CLINICAL FEATURES

Hepatitis C virus (HCV) is a RNA virus which is related closely to the flaviviruses but is unrelated to other hepatitis viruses [19,20]. A hallmark of HCV is genetic variability, manifested as differences in genotypes and quasispecies. Genotypes of HCV are major genetic groups which can have sequence variability as great as 35% [20]. There are six genotypes and more than 50 subtypes [20,21]. In Vienna, Austria, the prevalences of HCV genotypes 1, 2, 3, 4 and 5 in 250 patients (30% injection drug users) were 74.8%, 2.8%, 16%, 5.2% and 0.4%, respectively [22]. In 438 patients from 10 centers in the United States (24% injection drug users), the proportions of patients with genotypes 1, 2, 3 and 4 were 71.5%, 13.5%, 5,5% and 1.1%, respectively [23]. In a study of injection and non-injection

drug users from Flanders, Belgium, 48.7% had genotype 1, 1.4% had genotype 2, 41.2% had genotype 3 and 8.8% had genotype 4 [24]. Genotypes have a major impact on response rates to antiviral therapy for HCV infection, with genotypes 2 and 3 responding more often and with shorter treatment duration than genotypes 1 and 4. The distribution of genotypes is therefore of great importance in interpreting studies of antiviral therapy [20].

Quasispecies are a mixed population of HCV sequences within a given individual [20]. They are closely related but not identical. Quasispecies may contribute to the chronicity of HCV infection, the response or lack thereof to antiviral therapy and the difficulties in HCV vaccine development [20].

Injection drug use is by far the most significant risk factor for HCV infection in most developed countries. In an analysis of the 1999–2002 National Health and Nutrition Examination Survey (NHANES) from the United States [25], the adjusted odds ratio for the association of injection drug use with the presence of antibody to HCV (anti-HCV) was 148.9 [95% confidence interval (CI) 44.9–494]. In contrast, the adjusted odds ratio for blood transfusions before 1992 (the year that HCV screening of transfused blood was fully implemented) was 2.6 (95% CI 0.9–7.3). and for 20 or more life-time sexual partners it was 5.2 (95% CI 1.5–18.2) [25]. The prevalence of anti-HCV in the United States was found in this study to be 1.6%, corresponding to 4.1 million people. The prevalence of HCV-RNA-positivity, reflecting viremia and chronic infection, was 1.3%, corresponding to 3.2 million people. The true prevalence of chronic HCV infection may be higher, as the NHANES study did not include homeless or institutionalized people [25]. Also, the association of anti-HCV with injection drug use may be even stronger, as the memory of experimentation with drug injection may be suppressed, forgotten or withheld at the interview [26].

Sexual transmission of HCV is possible but inefficient. Within antibody-discordant couples, sexual transmission of HCV is rare [27–29]. In studies from the United States and Europe that used genotyping, the prevalence of the same genotype in non-injecting heterosexual partners of people with HCV-associated chronic liver disease is 2–3% [29]. In studies of injection drug users, sexual practices did not correlate with HCV infection [28,30,31]. Sexual transmission of HCV is much more likely, however, with co-infection with HCV and human immunodeficiency virus (HIV) [32,33].

Injection drug users have very high prevalences of anti-HCV, ranging from 53 to 96% [34–40]. Lower prevalences, 27–46%, are seen in younger patients [41,42]. HCV can be acquired rapidly by injection drug users, with 65% positive for anti-HCV after 1 year or less of injection drug use [35] and 77% positive after 1–2 years [30]. Among people injecting for 10 or more years 94% were positive for anti-HCV [30], and in current or former injection drug users with biopsy-proven chronic liver disease, 98% were positive [43]. Data from the early 2000s have revealed declines in the prevalence of HCV infection among injection drug users, attributed to increased awareness of risk factors for HIV and HCV infections, syringe exchange programs and availability of methadone maintenance treatment [44,45].

Studies in methadone maintenance programs conducted after initial enrollment reveal seroprevalences ranging from 67 to 96% [31,46–50]. Methadone maintenance treatment reduces and often eliminates heroin injection, and it therefore could prevent acquisition of HCV in those who are seronegative at the time they enter treatment [2,51]. Seroconversions to HCV during methadone maintenance treatment are due to injection of heroin or other drugs, often as a result of inadequate methadone dose or interruption of treatment [36,48,52].

Acquisition of HCV infection is subclinical in most patients [53]. Acute HCV infection is diagnosed infrequently, but as anti-HCV does not confer protective immunity more than one

episode may occur in a person with multiple exposures [54]. Fulminant HCV infection is very rare [55].

Chronic HCV infection occurs in 55–85% of any group of exposed people [56,57]. HCV infection is characterized by continuous viral replication and rarely resolves spontaneously [53]. Serum transaminases are normal or mildly elevated and may fluctuate over time. Transaminase abnormalities with minimal or no symptoms are often the initial finding. Chronic HCV infection leads usually to hepatic necroinflammation and fibrosis, assessment of which requires liver biopsy. Transaminase levels correlate poorly with liver biopsy findings. Some patients with normal transaminases have significant liver fibrosis [58,59]. In most United States methadone clinics, routine testing is only with liver transaminases for cost containment, and cases of HCV infection are missed [60].

After 20–30 years of chronic HCV infection, 5–20% of persons will progress to cirrhosis [59]. Hepatocellular carcinoma may develop in patients with cirrhosis and HCV infection at a rate of 1–4% per year [53]. Cirrhosis from chronic HCV is the most common indication for liver transplantation [61]. Hepatic cirrhosis has been found to be more common in users of both alcohol and drugs by injection compared with users of alcohol alone or drugs by injection alone [62,63]. Many studies have shown that liver fibrosis in chronic HCV infection progresses more rapidly in patients with significant use of alcohol [64–67]. Even moderate drinking (20–50 g alcohol daily) may increase the rate of liver fibrosis in chronic HCV infection [64,68]. Alcohol use reduces responsiveness to antiviral therapy for HCV infection [66,69]. A safe level of alcohol intake for patients with HCV infection has not been established [66,67], and abstinence from alcohol is the best advice for patients with this disorder. Age greater than 50 years at the onset of HCV and male gender are also important factors in fibrosis progression [70]. In HCV-infected patients who also have chronic hepatitis B virus infection, there may be more severe chronic liver disease and an increased risk of hepatocellular carcinoma [71].

TREATMENT OF HCV INFECTION

Antiviral therapy of chronic HCV infection is improving. Interferon monotherapy was the earliest regimen followed in the late 1990s by combination treatment with interferon and ribavirin. Recent advances have involved pegylated interferons. The attachment of polyethylene glycol to the interferon molecule results in reduced clearance and prolonged half-life, allowing once-weekly dosing [72]. In addition, the wide fluctuations in plasma levels seen with standard interferon are avoided.

The primary endpoint of antiviral therapy for HCV infection is the SVR, defined as undetectable HCV-RNA 24 weeks after the end of treatment. The efficacy of treatment is also assessed using the rapid virological response, defined as undetectable HCV-RNA after 4 weeks of treatment, and the early virological response (EVR), defined as undetectable HCV-RNA or a decrease in HCV-RNA level of 2-log or greater at 12 weeks [73].

The currently recommended treatment is peginterferon α-2a 180 μg subcutaneously weekly or α-2b 1.5 μg/kg subcutancously weekly, plus oral ribavirin, 1000–1200 mg daily based on body weight. In a large clinical trial of 48 weeks of treatment, peginterferon α-2b plus ribavirin yielded a SVR of 54%, compared with 47% for interferon α-2b plus ribavirin [74]. Among genotype 1-infected patients, 42% responded to peginterferon α-2b and ribavirin versus 33% to interferon and ribavirin [74]. A study of peginterferon α-2a plus ribavirin given for 48 weeks showed a SVR of 56% in all patients and 46% in genotype 1 patients, results significantly better than in the comparison groups [75].

Some patients have improvement in liver histology after peginterferon treatment for chronic HCV infection despite failure to achieve SVR [74,76,77]. Also, pooled data in 3010 recipients of antiviral therapy for chronic hepatitis C who had pre- and post-treatment liver biopsies showed that treatment reduced the rate of progression of fibrosis and the incidence of cirrhosis [78]. This effect was most common in patients who had a SVR, but also occurred in others. In patients with cirrhosis on their initial biopsy, improvement in fibrosis ('reversal of cirrhosis') was seen in 49% [78]. Only one-third of those had a SVR.

Patients with genotype 1 should receive 48 weeks of therapy for HCV as long as they achieve an EVR. Discontinuation of antiviral therapy should be considered strongly if EVR is not achieved, but more prolonged treatment may be helpful [73] for those with cirrhosis or bridging fibrosis (liver biopsy showing connective tissue bridges that link portal tracts with other portal tracts or central veins, but no regenerative nodules indicating cirrhosis) [79]. Patients with genotypes 2 or 3 can be treated with 24 rather than 48 weeks of peginterferon and ribavirin and a lower dose of ribavirin, 800 mg daily [80]. A SVR rate of 84% has been reported with this regimen [80]. Extensive research is in progress to develop new and improved therapies [57,59]. Recent studies have suggested that treatment efficacy may be enhanced by prolonging antiviral therapy to 72 weeks in genotype 1 patients who have detectable HCV-RNA at 4 or 12 weeks but none at 24 weeks [73,81,82].

Side effects of peginterferon and ribavirin include flu-like symptoms, anemia, neutropenia and thrombocytopenia [83]. The flu-like symptoms caused by interferon may resemble opiate withdrawal. Methadone disposition is not altered significantly by peginterferon α-2a [84] or α-2b [85,86]. Peginterferon can cause psychiatric symptoms, including malaise, irritability and depression [83]. Family members and opioid treatment program personnel can be enlisted to help monitor for these symptoms, Rarely, acute psychosis, suicide attempts or completed suicides have occurred in patients without addictive diseases receiving interferon products. Severe psychiatric symptoms necessitate discontinuation of therapy, but milder ones can be managed with antidepressants and possible peginterferon dose reduction. Psychiatric consultation is not mandatory in all cases of depression, but will often be helpful [87]. Ribavirin is contraindicated in pregnancy, and males should not father children while taking the drug and for 6 months following treatment.

Although one study suggested that superinfection with hepatitis A virus may increase the risk of fulminant hepatitis in patients with chronic HCV infection [88], others have not confirmed this [89]. Hepatitis A [89] and B [90] vaccinations of susceptible HCV-infected patients are recommended.

In June 2002, the US National Institutes of Health (NIH) convened a Consensus Development Conference on hepatitis C [58]. The conference report recommended increased consideration for antiviral therapy of patients in methadone maintenance treatment, injection drug users who are likely to comply with therapy, and patients with co-infection with HCV and HIV. All patients are potential candidates for treatment, but those with little or no fibrosis may reasonably choose observation.

Table 1 shows the results of treatment of HCV-infected methadone maintenance patients with interferon or peginterferon and ribavirin. Two studies included some buprenorphine-maintained patients [13,14]. The rates of SVR in maintenance patients in these reports ranged from 28 to 94%. Three studies assessed the statistical significance of the SVR rate in methadone maintenance patients versus contrast groups, and all found no difference [7,9,15]. In one report [9], methadone maintenance patients had a higher rate of discontinuation of antiviral therapy in the first 8 weeks but not subsequently. In the other five studies, 72–100% of maintenance patients completed antiviral therapy. None of the

three papers with contrast groups showed an increase in psychiatric side effects in methadone maintenance patients [7,9,15]. Sylvestre *et al.* reported a modest decrease in SVR rate in patients with a pre-existing psychiatric history [10].

The quality of this published work on antiviral therapy of HCV in methadone maintenance patients is variable. As Mauss *et al.* indicate, a randomized trial comparing HCV treatment in patients on, versus not on, opioid maintenance, is not feasible [9]. Five of the papers listed in Table 1 provided inclusion and exclusion criteria, and one did so partially [13]. In two [7,1 5] of the three studies with contrast groups there were some baseline differences between the methadone and contrast groups. Mauss *et al.* matched control patients for sex, age, HCV genotype and HCV-RNA [9]. Five of the six studies used an ITT analysis. One group from Norway planned to study all genotypes but decided later to publish data only on genotype 3, the predominant genotype there, because only three non-genotype-3 patients were enrolled [14]. Four reports described withdrawals and dropouts adequately, one did so partially [15] and one had no dropouts [14]. Three studies compared methadone patients with and without SVR [9,10, 15]. None address the issue of HCV re-infection after SVR; a few studies of this in drug users who continue to inject describe a low incidence [91,92].

We conclude that the literature strongly supports the feasibility of antiviral therapy in methadone maintenance patients with HCV infection. This treatment can be effective, but additional studies with larger numbers would allow stronger conclusions regarding efficacy. Future studies should ideally be prospective; should have the study of methadone patients as a specific aim; should include data on the numbers of patients who were evaluated, were eligible for the treatment and who actually entered the study; should compare patients with and without SVR; and should have a prolonged follow-up. There is no scientific or clinical reason to withhold antiviral therapy from methadone or buprenorphine maintenance patients. Three groups have reviewed antiviral therapy for HCV infection in current or former injection drug users, and all support increased efforts to treat such patients [87,93,94].

HIV AND HCV CO-INFECTION

Injection drug use is a major route of transmission of both HIV and HCV. Overall, about 15–30% of HIV-positive individuals are co-infected with HCV [95,96]. In methadone maintenance patients, the prevalence of HIV and HCV co-infection will be significantly higher because, as discussed previously, 67–96% of methadone maintenance patients are infected with HCV [31,46–50]. A small number of patients with HIV infection may be seronegative for anti-HCV despite having HCV infection with HCV-RNA positivity [97]. Compared with HCV alone, HIV and HCV co-infection is associated with higher HCV-RNA levels [98,99] and a more rapid progression to cirrhosis [98–100]. Co-infected patients who are treated with antiretroviral therapy are living longer and arc thus more likely to develop complications of, and mortality from, HCV-associated liver cirrhosis [101].

Several of the antiretroviral medications used to treat HIV infection may cause hepatotoxicity, which may be manifested as asymptomatic elevations of liver transaminases or, less frequently, clinical hepatitis [102]. Nevirapine commonly causes clinical hepatitis, and some cases may be part of a hypersensitivity syndrome including rash, fever and eosinophilia [102]. Nucleoside reverse transcriptase inhibitors used to treat HIV infection can cause a syndrome of lactic acidosis and hepatic steatosis that has a high mortality [102,103]. In HIV-infected patients receiving protease inhibitors, co-infection with HCV is associated with an increased risk of hepatoxicity which is thought to be secondary to toxic metabolites [104,105] or immune reconstitution from effective HIV therapy [102]. Several of the medications used to treat HIV infection have significant interactions with methadone; these have been comprehensively reviewed elsewhere [106–108].

Antiviral therapy for HCV can be effective in patients with HIV/HCV co-infection. In three studies of 48 weeks of treatment, peginterferon α-2a or α-2b plus ribavirin was superior to interferon plus ribavirin in patients infected with HIV and HCV [109–111]. In genotypes 2 and 3, a full 48 weeks of antiviral therapy is recommended for HIV/HCV co-infection [109,112]. Antiviral therapy of HCV infection may be discontinued in co-infected patients who do not achieve an EVR [113]. Control of HIV disease is generally maintained during treatment of HCV infection with peginterferon and ribavirin.

For most patients with HIV/HCV co-infection, treatment of HIV with effective antiretroviral therapy will be the first priority. A recent study suggests that enrollment in methadone maintenance treatment can lead to improved adherence to antiretroviral therapy [114]. In early HIV infection, or when there is no HIV viremia, therapy for HCV infection may be initiated. Patients with HIV/HCV co-infection and CD4 counts under $100 \times 10^6/1$ should not be treated with antiviral therapy for HCV infection because interferon-induced myelosuppression may cause further decreases in CD4 counts leading to opportunistic infections [115]. In co-infected patients who receive peginterferon and ribavirin, clinicians will need to watch for drug interactions and overlapping toxicities. Ribavirin inhibits phosphorylation of zidovudine and stavudine *in vitro* [102,112,116], and these combinations are best avoided. Caution is recommended with the combination of ribavirin and didanosine because of increased mitochondrial toxicity (lactic acidosis and hepatic steatosis or chronic hyperlactatemia) [103,111,112]. In one study of HIV/HCV co-infection, peginterferon monotherapy was found to be more effective than standard interferon plus ribavirin [109], and this may be considered in selected patients in whom avoidance of ribavirin is desirable.

LIVER TRANSPLANTATION

Liver transplantation may be the only treatment option for patients with end-stage cirrhosis. In 2000, Koch & Banys surveyed liver transplantation programs in the United States and found that although 56% accept methadone maintenance patients, another 32% require that methadone be discontinued prior to transplantation [117]. This practice has been criticized appropriately in editorials in transplantation journals [118,119]. Such a requirement would enhance the likelihood of relapse to heroin use [52,120] and should be discontinued. Thirty-nine programs had transplanted one or more methadone maintenance patients, with a total of 180 patients transplanted, but only nine programs had transplanted more than five such patients [117].

Small numbers of liver transplantations in methadone maintenance patients [121–124] have been reported (Table 2). Liu *et al.* described 36 such patients, all but one of whom had HCV infection [122]. Postoperatively the methadone dose had to be increased in 15 and decreased in four [122]. Four patients experienced single episodes of relapse to heroin use, and the methadone dose was increased in two of these. Nine patients died (median follow-up 999 days, range 208–2561), but none of the deaths were associated with heroin use or methadone treatment. Patient and graft survivals were comparable to national averages at 1, 3 and 5 years [122]. Weinrieb *et al.* described 10 methadone maintenance patients who were transplanted, and they found that these patients required significantly higher doses of intraoperative anesthesia and postoperative analgesia than transplanted patients not receiving methadone [123]. Their paper includes detailed recommendations on effective analgesia for methadone maintenance patients in the transplant setting [123], Methadone doses were increased in 50% of their patients, and the average dose increase was 60%. Two of the 10 patients had post-transplant substance abuse, one with alcohol and one with cocaine. Kanchana *et al.* describe serious postoperative complications in four of five patients, but none relapsed to substance use [121].

Chronic hepatitis C almost always recurs in liver transplant recipients [125,126]. Infection of the new liver is associated with rapid progression of chronic hepatitis, with a median time to cirrhosis of 8–10 years, and antiviral therapy is often tolerated poorly [125,126]. The two larger studies of liver transplantation in methadone maintenance patients [122,123] describe severe recurrent HCV disease (Table 2). A methadone maintenance patient who was treated successfully for HCV which recurred after liver transplantation has been reported [124].

A liver transplantation program from Barcelona, Spain, has reported selection criteria for HIV-infected patients with end-stage liver disease from HCV or hepatitis B which indicate that methadone maintenance patients are being accepted [127,128]. A consensus document supporting the policies of this program has been published [127].

These data suggest that successful liver transplantation is achievable in methadone maintenance patients. It is likely that many methadone maintenance patients in the developed countries with end-stage cirrhosis are not being referred for liver transplantation, and further research is therefore indicated. The roles of antiviral therapy [129] and re-transplantation [130] for all transplanted patients with HCV need further clarification.

METHADONE-RELATED ISSUES

Methadone maintenance treatment has been an effective treatment for heroin addiction for more than 40 years [131] and has shown to be non-hepatotoxic [132] and safe when administered up to 15 years or longer [133], Long-term methadone maintenance can normalize several parameters of cellular immunity which become abnormal during injection drug use [134]. Methadone disposition is not altered significantly in moderate [135] and most cases of severe [136] chronic liver disease. This is attributed to a balance between damage to hepatic drug-metabolizing systems and damage to the storage and release functions of the liver regarding methadone [135,136]. The optimal methadone dose (80–1 50 mg) need not be changed in patients with stable chronic liver disease, including advanced cirrhosis. Higher doses of methadone (> 120 mg) in maintenance treatment are probably safe, but have not been studied prospectively. Doses of 120–150 mg have been used extensively world-wide: some groups use doses >150 mg. Optimal management of patients with doses >120 mg includes measurement of plasma methadone levels and monitoring of the corrected QT interval [137].

Buprenorphine with naloxone can be an effective treatment for opioid dependence [45]. Sullivan *el al*. compared patients entering buprenorphine treatment with and without prior methadone maintenance and found that the latter had fewer years of opioid dependence and thus a lower prevalence of anti-HCV [138]. They suggest that buprenorphine treatment may attract some patients with more recent narcotic use, allowing for prevention of some cases of HCV infection.

We have described the high quality of medical care, and the support in the medical literature thereof, which can be provided to methadone maintenance patients with HCV infection. The current reality for most patients falls far short of the treatment we have reviewed. There are many barriers to treatment of HCV infection in current or former injection drug users [87,139–145]. Patients may have incomplete knowledge and understanding of HCV disease and may not know of available resources for HCV treatment [139,145]. They may be unaware of their personal status regarding HCV, HIV or other health issues [139,145]. Other medical or psychiatric conditions, use of illicit drugs or alcohol, lack of adequate housing or legal difficulties may reduce interest in, or adherence to antiviral therapy [87,141–143]. Other patient-related barriers include distrust of the health-care system, difficulties with transportation to treatment sites, fear of adverse effects and penalties for missed visits [140,143,144]. The cost of testing, including multiple quantitative HCV-RNA

determinations, medications and medical services, including liver biopsy, can be a major barrier [60,144]. Brown *et al.* analyzed the availability of services for HCV in a network of treatment programs in the United States that participate in a National Institute on Drug Abuse program to improve addiction treatment [60]. They found that only 74.1% offered patient education on HCV, 34.4% of programs offered HCV testing, 58.9% offered HCV counseling and 28.9% offered HCV treatment [60].

Notwithstanding the dedicated and capable physicians and staff involved with addiction and HCV patients, some providers may have negative attitudes regarding treatment of drug users or may be inexperienced in such treatment [87,143,144]. They may believe that current or former drug users will adhere to treatment poorly [143,144]. Finally, despite a United Nations position paper [146] and a National Institutes of Health Consensus Conference [147] supporting expansion of methadone maintenance or buprenorphine/naloxone treatment in areas of need, such treatment is not consistently available.

Some research has been conducted on overcoming barriers to HCV treatment in current or former injection drug users. Hallinan *el al.* studied patients with chronic HCV on opioid replacement therapy with methadone or buprenorphine in Australia [148]. Using personnel trained in HCV, they found that 27 of 43 (63%) patients referred to a liver clinic had attended it, despite multiple barriers. Moirand *et al.* found that among 378 patients with a history of injection drug use, enrollment in methadone maintenance was associated with initiation of anti-HCV therapy [149]. Sylvestre *et al.* treated 76 methadone-maintained patients at two drug-treatment facilities which provide comprehensive primary care for medical and psychiatric problems [10]. Prior to antiviral treatment, 36 (47%) were taking antidepressants compared with 65 (86%) at the end of treatment. They conclude that HCV treatment can be successful in methadone patients in a setting that can address their special medical and psychiatric needs. Sylvestre & Clements reported that adding new psychiatric medications improved HCV treatment adherence [150]. Schaefer *et al.* found that 67% of patients on methadone maintenance received antidepressants during HCV treatment [15]. Their study utilized an interdisciplinary team and thorough pretreatment medical and psychiatric evaluations. In Norway, provision of psychosocial support and a multi-disciplinary team resulted in 100% adherence to antiviral therapy; however, all patients had genotype 3 and therefore needed only 24 weeks of therapy [14]. Watson *et al.* found that a structured alcohol brief intervention was acceptable to opioid maintenance patients with HCV and alcohol misuse [151].

Overcoming the barrier of inadequate funding is a challenge in many countries. Mauss *et al.* found that most methadone patients who discontinued antiviral therapy did so within the first 8 weeks, limiting the cost of unsuccessful treatment [9]. A study of methadone maintenance patients in New Zealand indicates that peginterferon and ribavirin for HCV are cost-effective under varying assumptions of rate of disease progression and adherence to treatment [152].

CONCLUSIONS

We conclude that antiviral therapy for HCV can be provided to methadone maintenance patients with acceptable rates of adherence and SVR. When one considers the multiple barriers to such treatment, including underlying psychiatric disorders, the available results compare favorably to those of the initial drug trials, in which methadone patients were excluded. Data suggest that effective treatment of psychiatric disorders, a multi-disciplinary team and a treatment site that is acceptable to methadone maintenance patients (often but not necessarily the site of methadone treatment) will improve results. Controlled studies to prove conclusively that these measures are effective are not likely to be forthcoming. Liver

transplantation can be effective in methadone maintenance patients with advanced liver disease and should be utilized more widely. Advances are needed in financial support, greater access to addiction treatment, additional research on outcomes of antiviral therapy and liver transplantation, data on immunological and genetic aspects affecting response and development of a HCV vaccine. This review is most applicable to the developed countries. Studies are needed in less developed countries in which methadone maintenance is being introduced for the treatment of addiction and to reduce the incidence of HIV and HCV infection.

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Table 1

Prospective studies of antiviral therapy for chronic hepatitis *C* virus infection in methadone maintenance patients.

Author and country	n (methadone)	Contrast group	n (contrast)	Genotype (methadone) 1	2	3	4	Genotype (contrast) 1	2	3	4	Medication	Dosage	SVR (methadone)	SVR (contrast)	Completion rate (methadone)	Completion rate (contrast)	Methadone dose increase
Sylvestre *et al* (2002, 2005) [6,10], United States	76	None		60%	13%	25%	0%					IFNα 2b Ribavirin	3 mu t.i.w. 1000–1200 mg daily	28%		76%		45%
Schaefer *et al.* (2003) [7], Germany	21	Psychiatric disorder[1]	16	28%	10%	62%	0%	69%[1]	0%	25%	6%	IFNα 2a Ribavirin	3 mu t.i.w. 1000–1200 mg daily	48%	38%[1]	86%	82%[1]	38%
		Former IDU[2]	21					43%[2]	10%	43%	4%				28%[2]		57%[2]	
		No addiction or psychiatric history[3]	23					66%[3]	13%	17%	4%				35%[3]		87%[3]	
Mauss *et al.* (2004) [9], Germany	50	No IDU history for at least 5 years	50	58%*	42%*			58%*	42%*			PEG IFNα2b Ribavirin	1.5 μg/kg weekly 1000–1200 mg daily	42%	56%	50%†	76%†	‡
Belfiori *et al.* (2007) [13], Italy	24§	None		50%	0%	42%	8%					PEG IFNα2b Ribavirin	1.5 μg/kg weekly 1000–1200 mg daily	29%		75%		n.n.
Krook *et al.* (2007) [14], Norway	17§	None		0%	0%	100%	0%					PEG IFNα2a Ribavirin	180 μg weekly 800 mg daily	94%		100%		¶
Schaefer *et al.* (2007) [15], Germany	18	Psychiatric Disorder[1]	22	39%	6.5%	50%	5.6%	77%[1]	0%	23%	0%	PEG IFNα2b or PEG IFNα2a	1.5 μg/kg weekly 180 μg weekly	72%	50%[1]	72%	91%[1]	n.n.
		Former IDU[2]	13					46%[2]	0%	54%	0%	Ribavirin	800–1200 mg daily		54%[2]		85%[2]	
		No addiction or psychiatric history[3]	17					82%[3]	0%	18%	0%				59%[3]		94%[3]	

IDU = injection drug use; IFN = interferon; SVR = sustained virologtcal response (negative HCV-RNA 24 weeks after the end of treatment.); t.i.w. - thrice weekly; PEG = peginterferon: n.n. = no information given.

*Genotypes 1 and 4 and genotypes 2 and 3 were combined in this study.

†Results are significantly different ($P = 0.01$).

‡Average methadone dose decreased by 5 mg in those who completed antiviral therapy.

§Includes buprenorphine patients: 38% in Belfiori *et al.* [13] and 18% in Krook *et al.* [14].

¶Average methadone dose increase of 20 mg. The superscript numbers 1, 2 and 3 serve to link data from each of the three contrast groups in both studies by Schaefer *et al.* [7].

Table 2

Liver transplantation in methadone maintenance patients.

Author and country	No. of patients transplanted	No. with substance abuse post-transplant	Methadone dose changes	Comments
Kanchana *et al.* (2002) [121], United States	5	0	One patient weaned off methadone	Good compliance with medications and follow-up. Postoperative complications in 4
Liu *et al.* (2003) [122], United States	36	4	Increase in 15 Decrease in 4	Nine deaths at 208–2561 days post-transplant; 5 deaths due to graft failure from recurrent HCV
Weinrieb *et al.* (2004) [123], United States	10	2	Increase in 5	Recurrent HCV with complications in 60%
Hancock *et al.* (2007) [124], United States	1	0	Increase during antiviral therapy	Recurrent HCV resolved after antiviral therapy